EDITORIAL

Nr 2020;10 (4):548-552

The Role of Hyaluronic Acid Injection for the Treatment of Tendinopathy

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DOI:
10.32098/mltj.04.2020.01

SUMMARY
Hyaluronic acid has carved out an essential, though sometimes discussed, role in the treatment of joint degenerative pathology. Recent studies, first in vitro, then preclinical, have paved the way for use in tendon pathology. Clinical experience to date has shown extremely encouraging results in different tendinopathy frameworks such as tenosynovitis, insertional tendinopathies and tendon mid-portion.

KEY WORDS
Hyaluronic acid; injection therapy; tendinopathy; tendon pathology; tenocytes; therapeutic option.

INTRODUCTION

Hyaluronic acid (HA) plays a key role in the joints, where it maintains the functional and metabolic interaction between synovial membrane, synovial fluid, cartilage and, indirectly, subchondral bone.
In the past, this molecule was extracted from rooster combs after grinding and chemical treatment, while today is mainly produced through bacterial fermentation processes (1, 2).
Most of the physiological effects of exogenous HA and its viscosity depend primarily on the molecular weight of the molecule, consequently influencing its possible applications (3, 4).
Intra-articular hyaluronic acid (HA) injections are widely used in the conservative treatment of osteoarthritis and could delay surgical treatment (5, 6).
The efficacy is related to possible disease-modifying effects, secondary to modulation of inflammatory response and to the direct and indirect effect on synovial tissue, bone and cartilage (7-16).
Recently, the interest about the applications of HA in tendon pathologies is increasing. This could be in part related to the emerging preclinical evidences on the interaction with tenocytes and tendon behaviour and in part to the increased use of ultrasound (US). Indeed, US allows better accuracy, helping to achieve better outcomes also for less approachable locations. Our US-guided technique permitted a real-time visualization of the needle during the procedure, ensuring the correct distribution of the product, with low-risk of failure to inject in the desired area.
In this brief editorial, we present, according to ethical standard of the journal (17), the state-of-art of the growing body of evidences in the field and the possible implications in clinical practice.

IN VITRO AND PRE-CLINICAL STUDIES

In recent years, several Authors have investigated the effects of HA on tendon cells relating to biomechanics, cell regeneration and proliferation.
Multiple findings support the role of HA in gliding resistance of tendon sheets decrease (18-21). The antiadhesive effect seems dose-dependent (20, 22).
Similarly, HA may determine increase tenocyte proliferation and vitality in a dose-dependent manner not related to molecular weight (23).
Anti-inflammatory properties of HA and its therapeutic biomolecular targets were also investigated.
Nakamura *et al.* compared the effects of corticosteroids and HA in human tendon fibroblasts from rotator cuff tears after surgical lesion. The Authors found that, both HA and corticosteroids induce anti-inflammatory and anti-adhesive effects on tendon and synovial fibroblast, whether cortico-

steroid cause biomechanical weakening of the torn rotator cuff tendons, causing apoptosis of the tendon fibroblasts at the ruptured sites (24).
Po-Ting Wu *et al.* showed that high molecular weight HA significantly downregulated the mRna and protein expression of MMP-1 and 3 in a dose-dependent manner, two major endopeptidases implicated in pain generation and tendinopathy cleaving ECM proteins and collagen (25).
Osti *et al.* tested different HA formulations, observing that HA enhanced viability, proliferation and expression of collagen type I in tendon derived cells from H_2O_2-induced oxidative stress, decreasing cytotoxicity, reducing Nrf2 expression and enhancing catalase recovery (26).
Several trials focused on the ability of HA to decrease adhesion formation in different animal models (27-29).
In a model of Achilles tendon rupture, healing time in the HA group was shorter probably due to the early termination of the inflammatory phase (30). Furthermore, the repetitive administration of sodium hyaluronate during the Achilles-tendon healing process could regulate angiogenesis increasing VEGF and type 4 collagen expression (31).
Repeated peri-patellar injections of HA in detrained patellar tendon may limit detrained-associated damage in tenocytes and maintain tenocyte anabolic activity during detraining (32). In a second study, Frizziero *et al.* showed that repeated peri-patellar injections of HA may maintain e structural and functional properties of patellar tendon and enthesis in detrained rats (33).

CLINICAL STUDIES

Rotator cuff tendinopathy

Meloni *et al.* found that ultrasound-guided HA injections in supraspinatus tendinosis may determine improvement in symptoms and disability until 9 months of follow-up compared to placebo (34).
Similarly, a 5-week HA injection protocol showed efficacy compared to placebo in rotator cuff partial tears in a placebo-controlled trial (35, 36).
Merolla *et al.* compared ultrasound-guided subacromial injections of HA and physiotherapy, founding that both treatments determine pain relief and clinical scores amelioration in the short term, while only HA group maintained a significant improvement at 12 weeks of follow-up (37).
Özgen observed that HA injection and physical therapy present similar effects in short and long term for supraspinatus tendinopathy (38). Flores *et al.* found that the combination of HA with an exercise protocol is superior to exercise only, leading to an earlier return to pre-injury activity and the need of less rehabilitation sessions (39).
Frizziero *et al.* found that both HA and low-energy ESWT are effective in improving joint function and reducing pain in patients with non-calcific rotator cuff tendinopathy until 3 months of follow-up, with no clinically significant difference (40).

Plantar fasciopathy

Two recent studies evaluated the effects of HA on plantar fascia pathology. Kumai *et al.* found that 5 ha injections determine symptoms relief with a dose-dependent improvement (41).
Raeissadat *et al.* compared ultrasound-guided Injection of high molecular weight HA versus corticosteroid observing that both corticosteroid and HA were effective in improving pain and function and decreasing plantar fascia thickness. However, corticosteroids seem to have a faster trend in the short term with no significant difference 24 weeks after the treatment between the groups (42).

Epicondylitis

In the study of Petrella *et al.* patients that received HA injections had significantly greater improvement in VAS pain at rest and after grip testing than control placebo group, that persisted to 1 year follow up (43).
Khan *et al.* observed that a single injection is effective in management of moderate pain (VAS score < 7), but not severe lateral epicondylitis (44).
Tosun *et al.* compared the effects of a combined HA- chondroitin sulphate injection versus a corticosteroid injection founding that both treatments were effective in reducing pain and improving function in short-term while HA was superior in long term follow-up (45).

Achilles tendinopathy

Lynen *et al.* compared safety and efficacy of 2 HA peritendinous injections respect to ESWT in mid-portion Achilles tendinopathy. HA injections showed greater outcome in short- and long-term with higher pain relief and function improvement until 6 months of follow-up (46).
Similarly, Fogli *et al.* and Frizziero *et al.* found that three US-guided HA injections induce prompt improvement in pain (NRS), symptoms and function (VISA-A, VISA-P and EQ-5D-5L) and US parameters (47, 48).
Good results were also reported in Ayyaswamy *et al.* with a single peritendinous injection of HA for non-insertional Achilles tendinopathy (49).

Patellar tendinopathy

Kumai found that a single HA was effective and safe in patellar entesopathy a week after treatment (50).
In accordance to Achilles tendinopathy, Fogli *et al.* and Frizziero *et al*. found that three US-guided HA injections induce prompt improvement in pain (NRS), symptoms and function (VISA-A, VISA-P and EQ-5D-5L) and US parameters (47, 48).
Kaux *et al*. compared platelet-rich plasma injections and hyaluronic acid injections under US guidance, evidencing that even both treatments could ameliorate symptoms, PRP group had significant improvement in quadriceps strength while HA seemed to have a prompt effect in pain-relief (51).

Tenosynovitis

Callegari *et al*. examined the efficacy and safety of ultrasound-guided HA and corticosteroid injection and compared with open surgery for the treatment of trigger fingers. Injection therapy was associated with a shorter recovery time, with a consequent reduced absence from sports and work activities and fewer complications (52). In accordance, other Authors found that HA achieved similar effect as steroid injection in trigger finger with a long-lasting functional improvement (MHQ scores continued to increase in the HA group at 3 months follow-up) without adverse events, until 6 months of follow-up (53, 54).
Orlandi *et al*. compared the 6 months outcome of three different ultrasound guided percutaneous injection treatment for de Quervain's disease (steroid alone, steroid with saline, steroid with HA). At 6-month follow-up, patients treated with steroids and HA injections had significantly better VAS score, quick DASH score and retinaculum thickness compared to other groups (55).

PERSPECTIVES

Therapies for tendinopathies keep changing as research in this field progresses. To date, different injective substances have been investigated: platelet-rich plasma, high volume image-guided injections, hyaluronic acid, and prolotherapy, as a suitable option beside the commonly used eccentric loading rehabilitation regimen (56).
Preclinical and clinical findings appear to be promising for hyaluronic acid, especially for Achilles and patellar tendon pathology.
Considering that pre-clinical findings suggest dose-dependent effect and most of clinical studies used repeated injections protocol, it seems that more than 1 injection should be considered in clinical practice to maximize the efficacy.
Actually, no clear indication about the correct molecular weight could be provided. In *in vitro* studies all the molecules were effective, while no comparison in clinical trials has never be performed to our knowledge. However, the rationale for HA in tendon is the possible effect on tendon cells, collagen structure and resistance gliding and we speculate that low to medium molecular weight may be prefer, considering that no "viscosupplementation" effect is necessary.
Further studies with large cohorts of patients for adequately long follow-up periods are needed to reinforce the present positive clinical results.

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